International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 11(1): January-February 2021

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Review Article……!!!**

Received: 29-11-2020; Revised: 25-01-2021; Accepted: 30-01-2021

SOLID DISPERSION: AN UPDATE ON ADVANCED GUIDE ON SOLUBILITY ENHANCEMENT

Pratibha Verma*, Seema Saini, Naresh Singh Gill

Department of Pharmaceutics, Rayat Institute of Pharmacy, Railmajra, Punjab.

Keywords:

Solubility Enhancement, bioavailability, solubility, poorly water soluble, Dissolution, solid dispersion, permeability

For Correspondence:

Pratibha Verma

Dr. Naresh Singh Gill

Department of Pharmaceutics, Rayat Institute of Pharmacy, Railmajra, Punjab

E-mail:

pverm240@gmail.com

ABSTRACT

From decade to decade, solubility becomes the exigent aspect for formulation oforal drug delivery systems of poorly aqueous soluble drugs, supremely biopharmaceutical classification system (BCS) class 2 drugs. Large number of drug candidates with paltry bioavailability and dissolution has been caught. This becomes point at issue for delivering these drugs by oral route, which solicits the apt formulation of these drug entrants. There are vast kinds of techniques which can overcome solubility issues and inflate the bioavailability. Among them, Solid dispersion has enthralled an attention and becoming a medium for enhancing the dissolution rate and elevating bioavailability levels of hydrophobic drugs. Solid dispersion with hydrophilic transporters can deflate these hitches. The most advisable drug entrants are the ones, which have least aqueous solubility as in biopharmaceutical classification scheme (BCS) class 2 candidates. Formulating the drugs as solid dispersions might reduce particle size, doctor up wetting issues because of usage of hydrophilic carriers, reduces in agglomeration and might even changes physical state of drug compound. Practically, there are some aspects which have to be considered while formulating solid dispersions such as choosing carriers, arrangement of drug in solid dispersion molecularly. There are so many carriers which can create solubility problems in solid dispersions because of their hygroscopic nature and high viscosity. So, the polymers which have low viscosity and are of hydrophilic nature can ameliorate bioavailability of poorly soluble drug candidates. Natural polymers are more salubrious because of easy availability, less toxicity and also economically beneficial as compared to synthetic counterparts. This article reflects various conventional techniques for preparing solid dispersions, draws together some contemporary approaches and reviews the effect of natural versus synthetic polymers on drug liberation and bioavailability.

1. INTRODUCTION

The formulation of poor water dissolvable drugs has been a challenging aspect faced by pharmaceutical scientists and it is anticipated to amplify the solubility of such drugs, as approximately 40% or additional of the new chemical entities (NCE) existence generated through drug discovery programs are poor aqueous soluble. Also with an emergence of combinatorial science and high throughput screening method give rise to the no. of poor water soluble compounds. [1, 2, 3] This becomes point at issue for delivering these drugs by oral route, as distribution of such drugs by this route associated with minimum bioavailability and deficient of dose proportionality. This inadequate bioavailability is due to low dissolution rates offered by such drugs which are controlled by surface area that they introduce for dissolution. Any drug when administered in solid dosage form, the deliverance of its active constituents is important so that it can dissolve in gastrointestinal fluids before its absorption. Consequently, improving dissolution rates is of big value which in turn leads to greater bioavailability and solubility.

Solubility is chemical property of the solute to dissolve in particular solvent. Drug is said to be highly solubleand highly permeable when maximum of dose of drug is soluble in ≤250 ml of water over a pH range of 1 to 7.5 and extent of absorption in humans is to be ≥90% of an administered dose. The USP and BP criterion of solubility is shown in table 1.1. Extent of solubility depends upon solvent used, temperature and pressure. It can be measured at equilibrium stage, where solution becomes saturated and further increase in solute will not increase its concentration in solution.

The Biopharmaceutical classification system (BCS) is a logical structure for grouping a drug substance dependent on its water solvency and porousness of intestine. As for BCS class II & IV drugs, the rate-limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so with increase in solubility ultimately increase the bioavailability of BCS class II & IV drugs. There are several methodologies to enhance solubility and dissolution rate, which are solubilisation, lyophilization, pH adjustment, salt formation, particle size reduction, complexation, solid solutions etc. Among all of these methods, solid dispersion shows potential approach to scientists right and proper to the straightforwardness of research and reproducibility of manufacturing procedure.[4, 5]

TABLE 1.1: USP and BP criteria

Definition	Parts of solvents required for one part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly	100-1000
Very slightly soluble	1000-10,000
Insoluble	>10,000

Drugs which are highly permeable and having least aqueous solubility are the biopharmaceutical classification system 2 (BCS 2) drugs.The Biopharmaceutics Categorization System is a framework, first introduced by *Amidon et al*, to understand the concept of absorption of drugs and to categorize them on the root of their water solvency and porousness of intestine. There are four classes under this system which is as follows. [6, 7, 8, 9]

TABLE 1.2: Biopharmaceutical classification system

CLASS 1 High solubility High permeability	**CLASS 3** High solubility Low permeability
CLASS 2 Low solubility High permeability	**CLASS 4** Low solubility Low permeability

To cope with solubility issues of BCS class 2 drugs, solid dispersion is one of the trickiest way. Other techniques get pale in front of solid dispersion. Various physicochemical characteristics of drug like solubility, particle size, polymorphs, crystalline structure, salt form etc. among them solubility is more crucial factor which have to be resolved for getting triumph over low dissolution rates. Other factors which have to be considered are formulation factors which are aqueous solubility of formulation, drug excipient compatibility, stability etc.

NOYES WHITNEY EQUATION

Noyes Whitney Equation provides an idea of pace of dissolution which can help improve the bioavailability of inadequately dissolvable drugs by giving several parameters.

$$dm/dt = AD(Cs-C_b)/h$$

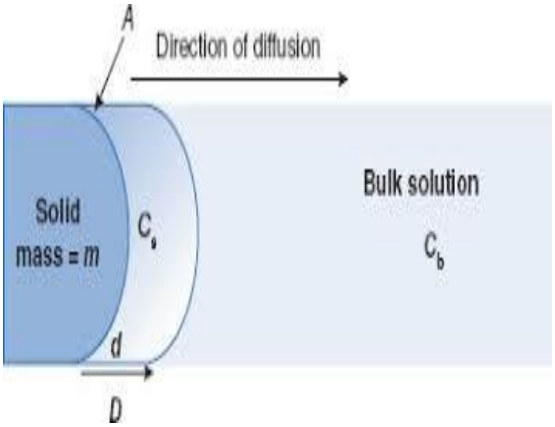

Figure 1.1: Noyes Whitney Parameters for Dissolution

dm/dt = rate of dissolution

A = surface area for dissolution

D = diffusion coefficient of the compound

Cs = concentration at surface

C_b = concentration in the bulk of the solution at time t

d = thickness of the concentration gradient. [10]

2. PROCESS OF SOLUBILISATION

The process of solubilisation is as follows,

- Breaking of inter-ionic and intermolecular bonds of the solute.
- The division of atoms in the solvent to give space to the solute molecules.
- Interaction among the solvent phase and the solute phase molecule or ion.[11]

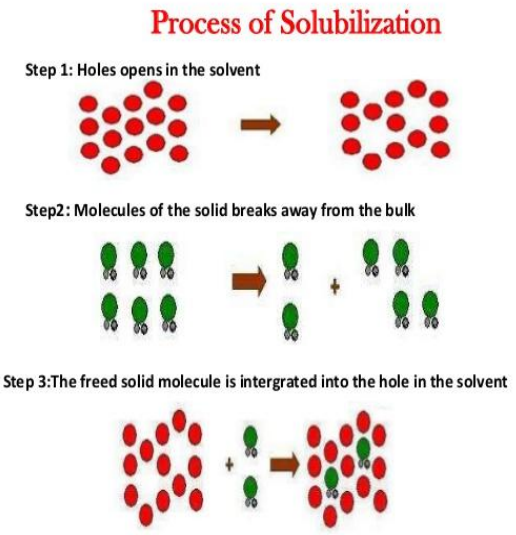

Figure 1.2: Process of Solubilisation

3. NEED FOR SOLUBILTY

For desired pharmacological action, high doses are required for poor aqueous soluble drugs after oral administration. For new chemical entities as well as generic drugs, low aqueous solubility is one of the major problems encountered. As water is solvent of choice, any drug to be retained at absorption site, it must be in aqueous solution. In BCS class II, drugs are highly permeable but least soluble. In this class, rate limiting steps are the liberation of drug from dosage form and their solubility in gastro intestinal fluid. So, it is required for class II drugs to increase their solubility to get

maximum bioavailability. Among new chemical entities produced by pharmaceutical industries, there are more than 40% entities are poorly aqueous soluble and have slow absorption which leads to variable bioavailability and cause gastrointestinal mucosal toxicity. A drug administered by oral route, water dissolvability is most important parameter to get desired pharmacological response.[4]

4. SUPREMACY OF SOLID DISPERSION

- Solid dispersion improves solubility of poor aqueous soluble drug candidates be reducing their particle size and ultimately increases the surface area and further ameliorate dissolution rate and bioavailability of hydrophobic drug.
- Hydrophilic carriers used in solid dispersion shows betterment in wetting of hydrophobic drug particles which improves solubility. Hence solid dispersion is a probationer of solubility.
- Amorphous form has better solubility than crystalline ones. Solid dispersion presents the drug in amorphous which is metastable polymorphic form and hence clears solubility issues.
- Solid dispersion improves porosity of drug molecules.[12]

5. CATEGORIZATION OF SOLID DISPERSION

On the basis of drug release mechanism, solid dispersion is classified into six types.[13, 14]

1. Simple Eutectic Mixtures

Eutectic system from the greek word "eu" means "well" and "texis" means "melting" which is a uniform mixture of compounds that diffuse and solidify at single temperature, the temperature which is lower than the melting point of the constituents. The eutectic temperature is the lowest temperature at which all the ratios of involved species will melt.After warming, lattice having low temperature will diffuse first,while the temperature of the blend has to enhance further for the wide range of various segment lattices to diffuse and melt. There are two phase in eutectic mixture.

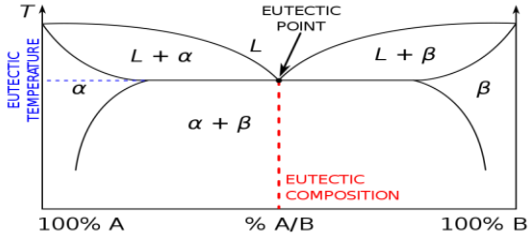

Figure 1.3: Binary phase diagram for a Eutectic

2. Mono-tectics

The monotectic system is same as eutectics but the only difference from eutectics is that it is having eutectic melting point which is coalescent with that of the pure material.

3. Solid Solutions

It is a system of poor aqueous soluble drug or solid solvent having solid solute dissolved in it which have good water solubility are comparable to liquid solutions and thus improving the drug dissolution to greater extent.

Depending upon the miscibility, there are two kinds of solid solutions.

- Continuous solid solutions – The no. of phases in this system is 1. The components are miscible at all proportions or compositions which show that the components are intensely and powerfully bonded than individual components.
- Discontinuous solid solutions – the no. of phases in this system are 2. This shows that components are partially miscible.

Depending upon the dissemination of the solvates, solid solutions are of two types.

- Substitution crystalline solution – They have crystalline structure. The solute molecule substitutes for the solvent molecule in crystal lattice or drug molecule substitutes for matrix.

  It may be continuous or discontinuous. No. of phases can be 1 or 2.

- Interstitial crystalline solid solutions – In this, dissolved molecules engaged into voids between the solvent molecules in the crystal lattice. These are of discontinuous type only. The no. of phases is 2.

4. **Amorphous Precipitations in the Crystalline Carrier**

These are high energy state systems in whichsolute molecules are molecularly scattered however irregularly with the amorphous solvent. They are generally not appear and are hardly ever encountered. No. of phases are 2.

5. Glass Solutions/Suspensions

A glass solution is a homogeneous system in which solute dissolves in a glassy solvent. The glassy state is characterized through transparency and brittleness beneath the glass transition temperature.

6. Complex Formations

In this system, drug and matrix interact with each other in aqueous phase so as to make a complex. During drug dissolution in the body, accessibility of the drug relies on solvency of drug, dissociation constant and intrinsic absorption rate constant. In correlation with inadequately soluble drugs, pace of dissolution and GI assimilation can be expanded by arrangement of soluble complex having low association constant.

On the basis of recent advancement, solid dispersion can be classifies as follows,[15]

1. First Generation Solid Dispersion

First generation solid dispersions can be prepared by crystalline carriers. Carriers such as urea and sugars were first used as crystalline carriers. But there are some cons of first generation solid dispersions that they are heat-labile and do not liberate drugs at faster rate because of crystalline nature of active ingredient which leads to low solubility and bioavailability.

2. Second Generation Solid Dispersion

For second generation solid dispersion, amorphous carriers can be used. The drug is distribute in the polymeric carrier which are of two types.

- Natural polymers – hydroxypropylmethylcellulose, starch derivatives like cyclodextrin.
- Synthetic polymers - polyethylene glycols and poly-methacrylates etc.

3. Third Generation Solid Dispersion

Surfactants or mixture of surfactants and amorphous carriers used for third generation solid dispersions. Such systems improve bioavailability of poor aqueous soluble drugs. Surfactants which were used in third generation solid dispersion are inulin, poloxamer 407 etcetera.

4. Fourth Generation Solid Dispersion

For such systems, poor aqueous soluble drugs with short biological half life are used. They are better known as CRSD (controlled release solid dispersion). In this system, drug is molecularly distributed in a carrier which improves the drug solvency and use of polymers which swell after coming in contact with aqueous environment, delays the liberation of the drug providing extended release of the drug in controlled manner. Polymers which were used in fourth generation solid dispersion are hydroxylpropyl cellulose, ethyl cellulose, Eudragits RS and RL, Polyethylene oxide Etcetera. Advantages of fourth generation solid dispersions are reduced dosing, patient acceptance, less adverse reactions and prolonged therapeutic effects of the drugs having short biological half life.

6. DIFFERENT TECHNIQUES FOR SOLUBILITY ENHANCEMENT

There are innumerable methods for preparing solid dispersion which are discuss as follows, [16, 17, 18]

1. Physical Modifications

- Comminution
- Co-crystallization
- Co-solvency
- Hydrotropic
- Solubilising agent
- Nanotechnology

2. Chemical Modifications

- Salt Formation
- Modification of crystal habit
- Complexation
- Solubilisation by surfactants
- Drug dispersion in carriers

1. Solid solution
2. Eutectic mixtures
3. Solid dispersion

3. Miscellaneous Methods

- Supercritical fluid method
- Spray freezing into liquid and lyophilization
- Evaporative precipitation into aqueous solution
- Solvent evaporation method
- Hot melt extrusion
- Electrostatic spinning method
- Direct capsule filling
- Polymeric alteration
- High pressure homogenization
- Lyophilization technique
- Inclusion complex
- Use of novel excipients

6.1 Comminution

Reducing the size of large unit masses into smaller unit masses or finer particles is known as size reduction or comminution or diminution. Solubility is inherently related with particle size. As reducing particle size will increase the surface area and provides better contact with the solvent and enhance the solubility. Equipments used for size reduction are Rotary Cutter mill, Ball mill, Roller mill, Fluid energy mill, Hammer mill. In these methods, physical stress is imparted upon drug product to cause degradation. Other techniques which are used for size reduction are spray drying, supercritical fluid process, and sono-crystallisation.

6.2 Nanosuspension

For hydrophobic drug entrants, Nanosuspension is the most propitious delivery systems. It is biphasic system, in which both water and oil insoluble drugs can be applied, consisting of pure poorly insoluble nano-sized drug particles which should be less than one micron (200-600 nm) surrounded by surfactant molecules, which helps in the stabilization. As particle size is reduced, it helps in increasing surface area and enhances the drug dissolution. Methods to prepare nano-suspensions are high pressure homogenization in water or in aqueous media, media milling, emulsion diffusion method, melt emulsification method.[19]

6.3 Modification of Crystal Habit

Polymorphism means to have more than one form. It is the ability of an object or element or compound to acquire more than one crystalline form. Different polymorphs have different physicochemical properties such as density, melting point, solubility; stability etc. One of the polymorph can be more physically stable than others. Depending on the stability, stable polymorph has least aqueous solubility because of low energy state and high melting point. Amorphous form of drug is most suitable for aqueous solubility because of high energy state and low melting point. Order of different solid forms of drug dissolution is as follows.[20]

Amorphous>Metastable polymorph>Stable polymorph

6.4 Cryogenic Techniques

Cryogenic techniques involve behaviors and production at extremely low temperatures (below 123K). It involves the use of liquefied gases like liquid nitrogen or liquid helium. In this techniques nano structured drug particles with highly porous structure are produced which helps in increasing the drug dissolution

6.5 Solid Dispersion

This concept was introduced by Sekiguchi and Obi, to enhance the dissolution and absorption of hydrophobic compounds. It is the dispersion of one or more active compounds (hydrophobic compound) in inert carrier (hydrophilic matrix) at solid state. Hydrophilic carriers which are commonly used are PEG 4000, PEG 6000, PVP K30, plasdone-S630, poloxamers etc. There are several methodologies for forming solid dispersions which are as follows.

6.5.1 Fusion Method

For preparing solid dispersion by fusion method, physical mixture of drug and aqueous soluble polymer is prepared and then heated directly until it transforms into melted mass. Then the molten mass is stirred continuously on an ice bath to solidify it, which is then crushed and passed into sieve of adequate aperture to get uniform granules which further dried in an air or in hot air oven in order to remove any residual moisture before punching into tablet.[21, 22]

6.5.2 Solvent Evaporation Method

Drug and carriers are dissolved in an appropriate solvent with continuous stirring until the complete solvent gets evaporated leaving behind thin, clear and solvent free film of drug and carrier. Film should be further dried, to get constant weight. Due to minimal temperature, there is no thermal decomposition of drug. But there are some cons of this technique too, like it is difficult to remove the solvent by evaporation, selection of solvent which must be volatile, higher cost, chemical instability due to possible adverse effects of solvent, difficulty in super saturation of solute in solid system.[23]

6.5.3 Melt Agglomeration Method

In this process, binder acts as carrier. Drug, binder, and other excipients are melted above the melting temperature of binder. Alternatively, a dispersion of drug is sprayed onto the warmed binder by using high shear mixing. This method will increase drug dissolution rates at low drug concentration. It was stated that melt-in method offers high dissolution rates than spray-on procedure with PEG-3000, Poloxamer 188. Melt-in procedures provides uniform dispersion of drug in agglomerate. [24]

6.5.4 Melt Solvent Method (Melt Evaporation)

This method is combination of melting and solvent evaporation method. The drug is first dissolved in suitable solvent and incorporated into melted carrier. The solvent is then evaporated to remove the moisture. Drugs which have high melting points can be easily incorporated into such solid dispersion methods.[25]

6.5.5Hot Melt Extrusion Method

Hot melt extrusion is a process of melting a polymer by applying heat and pressure and force it to pass through an orifice. Drug and carrier are melted together, homogenized and extruded with a twin screw extruder and shaped as pellets, sheets, tablets or powder. Drug and carrier are subjected to high temperature just for a short time as 1 minute which offers us an advantage but this somewhat enables a drug to be thermolabile to be processed. Extruder consists of four distinct parts, an opening for entering material into barrel, conveyer, and an orifice and auxillary equipment for cooling, cutting and collecting the product.[26]

6.5.6 Inclusion Complex Based Formation Techniques

This is the most precise technique among all other methods to improve aqueous solubility, dissolution rates and bioavailability of hydrophobic drugs. This method involves one guest molecule which is non polar moiety of molecule and one host molecule. Guest molecule is inserted into the host molecule which is cyclodextrin, most commonly used as host. [27]

6.5.7 Lyophillasation Technique

Lyophilization is an alternative to solvent evaporation technique. Drug and carrier are dissolved in an acceptable solvent and freeze in liquid nitrogen to shapelyophilized sub atomic dispersions. This method is most commonly used for thermolabile drugs and stable in dry state for prolonged storage conditions, but unstable in aqueous state.[28, 29]

6.5.8 Electrospinning

It is a combination of solid dispersion technology and nanotechnology. Solid fibers are made up of a polymeric stream and introduced through a millimeter scale nozzle. This method is advisable for nanofibers production and controlling the release of biomedicines. [30, 31]

6.5.9 Super Critical Fluid Technology (SCF)

When the temperature and pressure are over at its critical point, a substance is said to be in super critical stage. SCF can act as solvent or an anti-solvent in solid dispersion. It is primarily based on the principle that drug and carrier are dispersed in super critical solvent (e.g. CO2) and sprayed into an expansion vessel with lowest possible pressure. The rapid expansion initiates nucleation of dispersed drugs and carriers, prompting the development of solid dispersion with an appropriate size distribution in an exceptionally brief timeframe.[32]

6.5.10Spray Drying Method

This method is commonly used for thermo sensitive drugs. Feed solution is prepared by dissolving the drug in an appropriate solvent and carrier in water. The two solutions should be mixed by sonication until the clear solution is obtained. Firstly, the feed solution is sprayed in drying chamber via high pressure nozzle to frame fine beads. The formed droplets are comprises of drying fluid. Particles of nano or micro size will be formed with this technique.[32]

6.6 Complexation

Complexation is interaction between one or more compounds to form complex or non bonded entity. These interactions can be covalent or non-covalent. After complexation occurs, physicochemical properties of complex will be different from that of individual compound involve in complexation process. Complexing agent examples are EDTA, EGTA etc.[33]

6.7 Salt Formation

Almost entirely drugs are either weak acids or weak bases. To enhance their dissolution rates and solubility, the chief method is salt formation. In case of weak acids, strong basic salt is prepared. Example is sodium or potassium salts of barbiturates. For weak bases, strong acidic salt is prepared such as hydrochloride salts of several alkaloidal drugs. Resulting salt has more aqueous solubility than respective drug.[34]

6.8 Co-Solvency

Co-solvency means addition of another organic solvent which has capability to adequately change the solubility of drugs. Drugs which have non polar molecular or which are weak electrolytes are water immiscible. Addition of organic solvent improves their solubility. Process is also known as solvent blending. It is very rapid and uncomplicated process and also very high concentration of poorly aqueous soluble drugs can be easily dissolved.[19]

6.9 Hydrotropy

Hydrotropy is a process to enhance the water solvency of solute by adding excess amount of second solute. Compound which improves the solubility of hydrophobic solute is known as hydrotrope. Hydrotropic agents include sodium benzoate, sodium citrate etc.[19]

7. SUITABLE CARRIERS FOR PREPARING SOLID DISPERSION

7.1 IDEAL PROPERTIES OF CARRIERS[35]

- It must aqueous soluble for fast release and insoluble for sustained action.
- It should be thermo stable up to its melting point.
- It should be neither toxic nor irritant.
- It must be pharmacologically inert.
- It should not alter the physical and chemical properties of other ingredients.
- It should form complexes with the drug molecules.
- It must be economical.

7.2 SYNTHETIC CARRIERS[36]

7.2.1 Polyethylene Glycol (PEG)

PEG is a polyether compound known as polyethylene oxide or polyoxyethylene depending upon its melting point. Structure of it PEG is commonly expressed as H-(O-CH2-CH2) n-OH

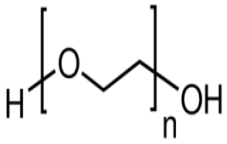

Figure 1.4: Structure of PEG

The term polyethylene glycol obtained by reacting ethylene glycol with ethylene oxide. PEGs with molecular weight above 30,000 are used as polyethylene oxides. PEGs are freely soluble in organic solvent which reflects its scrupulous advantage. PEGs aids in compound wettability. Melting point of PEG 1000 is 30-40 degree Celsius, the melting point of PEG 4000 is 5-58 degree Celsius, and the melting point is PEG 20,000 is 60-63 degree Celsius. But there are some cons of using low molecular weight PEGs that they concerns with toxicity problems.

7.2.2 Polyacrylates and Polymethacrylates

Copolymerization of acrylic and methacrylic acid produce tough, rubbery and vitreous polymer known as acrylates. They are known for their high transparency, have good impact toughness and elasticity, and have fairly good heat resistance up to ca. 450 K under dry heat. Trade name of polyacrylates is Eudragits.

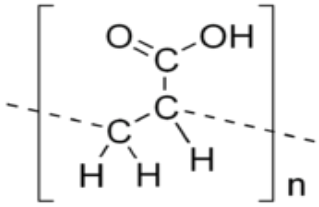

Figure 1.5: Structure of Polyacrylates and Polymethacrylates

7.2.3 Polyvinylpyrollidone (PVP) K30

Molecular weight of PVP is very high ranging from 10,000 to 7, 00,000. There is more consistent effect of molecular weight of PVP than PEG. The dissolution characteristics of drug will get decreased with increasing molecular weight of PVP, which ultimately increase viscosityand affects drug diffusion through viscous material into dissolution medium. PVP melting point is very high which about 275°C is. Owing to this, it cannot be incorporated into solid dispersion which prepared with fusion method.

7.3 NATURAL CARRIERS

IMPORTANCE OF NATURAL CARRIERS IN SOLID DISPERSIONS

To meet the industrial requirements and to reduce the production cost and hazardous effects of synthetic polymers, natural polymers has been continuously explored. Recently, many natural polymers have been investigated.

NEED FOR ALTERNATIVE CARRIERS

- Many carriers used in solid dispersion are hygroscopic in nature, which creates problem in large scale production.
- Polymers which give high viscosity do not offers greater solubility. So, the polymers which are of low viscosity and high swelling index can offers great outcomes of improving the drug dissolution and enhance solubility.

BENEFITS OF USING NATURAL POLYMERS

1.Low cost

2. Biocompatibility and biodegradability

3.Most of the polymers are hydrophilic in nature and after absorbing they swell and forms viscous gel layer around the dosage form resulting into delayed/sustained drug release.

MODIFICATION OF NATURAL CARRIERS[37]

There are several natural carriers have been scrutinized. But owing to their undesirable properties, they must be modified. Modification can simply done by placing a carrier in the porcelain dish and placed in hot air oven for a specified period of time and temperature, this will lead to changes in its characteristics like bulk density and tapped density, water holding capacity, flow properties, cars index, swelling index etc. and then carriers is sieved and stored in air tight containers. Charring of gums should be avoided which can alter active principles.

7.3.1 Locust Bean Gum (Modified)

Locust bean gum is a galactomannan obtained from seed carob tree i.e. ***Ceratonia siliqua***. Its structure is as follows.

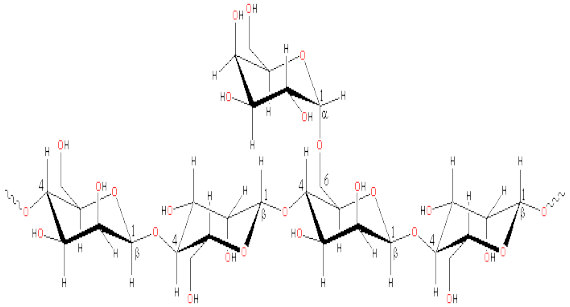

Figure 1.6: Structure of Locust Bean Gum

It was observed that heating at 140 degree Celsius, sample was charred and no further change in viscosity was observed by heating at 120 degree Celsius for 2 hours. So, the condition of heating at 120 degree Celsius for 2 hours was considered to be standard to prepare modified locust bean gum.

7.3.2 Xanthan Gum (Modified)

Xanthan gum is a microbial desiccation-resistant polymer prepared by aerobic submerged fermentation from ***Xanthomonas campestris***.

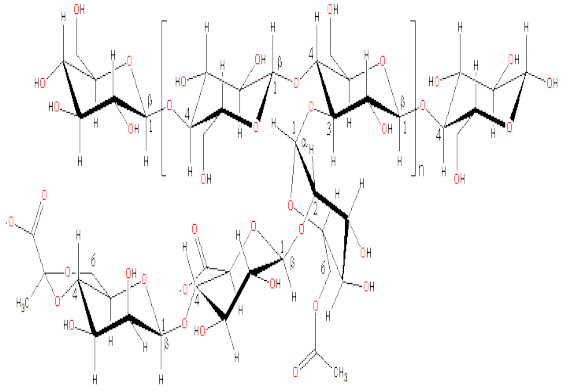

Figure 1.7: Structure of Xanthan Gum

Modification of xanthan gum can be done by heating at 120 degree Celsius. Heating at higher temperatures may decrease the swelling index and viscosity of modified xanthan gum than xanthan gum, reduce adhesiveness and may lose its structure.

7.3.3 Karaya Gum (Modified)

Gum karaya is an exudate of sterculia tree and it is comprises of polysaccharide sugars such as galactose, rhamnose and galacturonic acid

7.3.4 Hupu Gum(Modified)

Hupu gum or gum kondagogu is derived from Cochlospermum gossypium. Gum kondagogu belongs to the family Bixaceae. It is naturally occurring polysaccharide comprises of galacturonic acid, glucoronic acid, rhamnose, b-D galactopyranose, a-D-glucose, b-D-glucose, arabinose, mannose and fructose with sugar linkage. Modified hupu gum can be prepared by heating it at different temperatures which shows tremendous changes in its water holding capacity, swelling index cohesive and adhesiveness.

7.3.5 Guar Gum (Modified)

Guar gum is obtained from seeds of *Cyamompsis tetragaonolobus,* a leguminous plant Chemically, guar gum is galactomannan

polymer containing the sugars mannose and galactose.

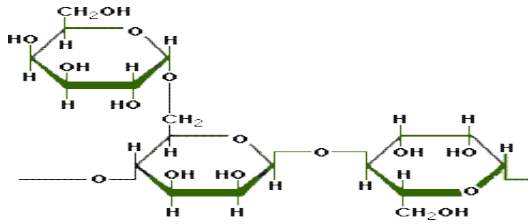

Figure 1.8: Structure of Guar Gum

Modification of guar gum is done by heating it at 120-130 degree Celsius for 2-3 hours. Modified guar gum has low viscosity than guar gum. The surface area of carrier expands upon coming in contact with aqueous environment which markedly improves dissolution and the dissolution rate.

SEMI-SYNTHETIC CARRIERS (CELLULOSE DERIVATIVES)[38]

7.4.1 Hydroxypropylmethylcellulose (HPMC) (Hyperomellose)

HPMC is a cellulose derivative. It is semi-synthetic, inert, viscoelastic polymer. It is solid, off white to beige powder in appearance. Its molecular weight is 10,000 to 15, 00000 It is a non fermented semi synthetic dietary fiber, based on cellulose, which is a carbohydrate consisting of anhydroglucose units.

7.4.2 Carboxymethylethylcellulose (CMEC)

CMEC is also a cellulose derivative. It can easily dissolve under alkaline conditions. CMECs are readily dissolved in acetone, isopropanol 70%, ethanol 60%.

7.4.3 Hydroxypropylcellulose (HPC)

It exhibit solubility in both aqueous and organic solvents. It is non ionic thermoplastic cellulose ether. Its molecular weight ranges from 37000 to 11,50,000.

8. OTHER CARRIERS

8.1 Sugars and Polyols Polymers

Sugars have good water solubility, but rarely soluble in organic solvents. They are less suitable because their melting point is very high and cannot be used in solid dispersion which are prepared with fusion method or melt method.

8.2 Organic Acids and its Derivatives

Some organic acids such as tartaric acid, phosphoric acid, succinic acid, citric acids canbe used to prepare solid dispersion.

8.3 Urea

Urea is the nitrogenous waste product of metabolism which is generated from breakdown of protein. It is freely soluble in organic solvents. Water solubility of urea is >1.

CONCLUSION

For poorly aqueous soluble drugs, dissolution is rate limiting step for oral absorption and solubility is an essential parameter for oral absorption in GIT. So, it is very crucial to carefully select adequate method of solubility enhancement to get maximum oral bioavailability, less frequent dose administration and better patient acceptance. Selection of method depends upon various drug characteristics such as, chemical nature, solubility, melting point, physicochemical nature, dosage form requirements like tablets or capsules, immediate or modified release dosage forms and regulatory requirements and so forth.

REFERENCES

1. Patil AN, Shinkar DM, Saudagar RB. Review Article: Solubility Enhancement by Solid Dispersion. International Journal of Current Pharmaceutical Research. 2017; 9(3): 15-18.
2. Patil RM, Maniyar AH, Akarte AM, Baviskar DT. Solid Dispersion: Strategy to Enhance Solubility. International Journal of Pharmaceutical Sciences Review and Research. 2011; 8(2): 66-73.
3. Huda NH, Saffoon N, Sutradhar KB, Uddin R. A review on Enhancement of Oral Bioavailability and Solid Dispersion. Journal of Applied Pharmaceutical Sciences. 2011; 1: 13-20.

4. Pawar AR and Choudhari PD. Novel Techniques for Solubility, Dissolution Rate and Bioavailability Enhancement of Class II & IV drugs. Asian Journal of Pharmaceutical Sciences. 2012; 1(3): 9-14.
5. Shiv M. Solubility Enhancement. A review. Journal of Pharmaceutical Sciences. 2009.
6. https://en.wikipedia.org/wiki/Biopharmaceutics_Classification_System
7. Wagh P. Millind, Patel S Jatin. Biopharmaceutical Classification system: Scientific Basis for Biowaiver Extensions. International Journal of Pharmacy and Pharmaceutical Sciences. 2010; 2(1): 12-19.
8. Mir K and Khan AN. Solid Dispersion: Overview of Technology. International Journal of Pharmaceutical Sciences and Research. 2017; 8(6): 2378-87.
9. Thakur N, Goswami M, Mittal P, Goyal P, Sood A. Solid Dispersion: A Novel Approach for Solubility Enhancement. International Journal of Pharmaceutical Review and Research. 2016; 39(1): 265-272.
10. https://www.pharmpress.com/files/docs/remington-education-physical-pharmacy-sample-chapter-3.pdf
11. Shinde, A, Solubilization of poorly water soluble drugs. Pharminfo. Net. 2007; 5(6): 44-52.
12. Allawadi D, Singh N, Singh S, Arora S. Solid Dispersion: A Review on Drug Delivery and Solubility Enhancement. International Journal of Pharmaceutical Sciences and Research. 2013; 8: 2094-2105.
13. Kumar B. Solid Dispersion- A Review. Reference ID. PHARMATUTOR-ART-2461. 2017; 5(2): 24-29.
14. Kamalakkannan V, Puratchikody A, Masilamani K, Senthilnathan B, Solubility enhancement of poorly soluble drugs by solid dispersion technique–A review. Journal of Pharmacy Research. 2010; 3: 2314-2321.
15. Singh G, Kaur I, Gupta GD, Sharma S. Enhancement of the Solubility of Poorly Water Soluble Drugs through Solid Dispersion. International journal of Pharmaceutical Sciences. 2017; 79(5): 674-687.
16. Yellela SR. Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. Journal of Bioequivalence & Bioavailability. 2010; 2(2): 28– 36.
17. Singh S, Baghel R, Yadav L. A review on solid dispersion. International Journal of Pharmaceutical Sciences. 2011; 2: 1078-1095.
18. Edward KH and Li D. Drug like Properties: Concept, Structure, Design and Methods, from ADME to Toxicity Optimization. Elsevier. 2008; 56.
19. Muller R, Jacob R and Kayser C, Nanosuspensions for the formulations of poorly soluble drugs. Pharmaceutical Emulsions and Suspensions, New York, NY: Marcel Dekker, Inc. 2005; 385: 2001.
20. TIMALSINA A, Karnataka Bangalore (Doctoral dissertation, Rajiv Gandhi University of health Sciences). 2015.
21. Dr. Seetha DA, Vasundhara K, Sultana MS. A Review on Solid Dispersions. World Journal of Pharmaceutical Research. 2018; 7(7): 665-692.
22. Tachibana T, Nakamura A. Colloid & Polymer Science. 1965; 203(2):130-133.
23. Sjokvist E, Nystrom C, Alde´n M and Caram LN. International Journal of Pharmacy. 1992; 79: 123-133.
24. Kumar SG, Naveen G, Babu AJ, Krishna GK, Reddy BR, Gopi K. A Review on Solid Dispersion and Its Application. World Journal of Pharmaceutical Research. 2019; 8(2): 340-354.
25. Rasenack N, Muller B. Microcrystals for dissolution rate enhancement of poorly water-soluble drugs. International Journal of Pharmaceutics. 2003; 254: 137-45.

26. Moyano JR, Blanco MJA, Gines JM, Giordano F. Solid-State Characterization and Dissolution Characteristics of Gliclazide-Betacyclodextrin Inclusion Complexes. International Journal of Pharmaceutics. 1997; 157(2): 239-243.
27. Dhirendra K, Lewis S, Udupa N and Atin K. Journal of Pharmaceutical Sciences. 2009; 22(2).
28. Morris KR, Knipp GT and Serajuddin ATM. Journal of Pharmaceutical Sciences. 1992; 81: 1185-1188.
29. Yu GD, Li JJ, Williams RG, Zhao M. Electrospun amorphous solid dispersions of poorly water-soluble drugs: A review. Journal of Controlled Release. 2018; 292: 91-110.
30. Kompella UB. Solid Dispersion a Promising Novel Approach for Improving the Solubility of Poorly Soluble Drugs. Critical Reviews in Therapeutic Drug Carrier Systems. 2001; 18(2): 173-199.
31. Subramaniam B. Phospholipid-stabilized nanoparticles of cyclosporine a by rapid expansion from supercritical to aqueous solution. Journal of Pharmaceutical Sciences. 1997; 86(8): 885-890.
32. Gupta S, Srivastav S, Vajpai M. Solid Dispersion a Promising Novel Approach for Improving the Solubility of Poorly Soluble Drugs Journal of Pharmacy Research. 2010; 3(4).
33. Kumar A, Sahoo SK, Padhe K, Kochar PPS, Satpathy A, Pathak N. Review On Solubility Enhancement Techniques ForHydrophbic Drugs. PharmacieGlobale International Journal of Comprehensive Pharmacy, 2011; 2(3): 1-7.
34. Sajid MA and Choudhary, V.Solubility enhancement methods with importance of hydrotropy. Journal of Drug Delivery & Therapeutics. 2012; 2(6): 96-101.
35. Duong VT, Mooter DVG. The role of the carrier in the formulation of pharmaceutical solid dispersions. Part II: amorphous carriers. National Library of Medicines. 2016; 13(12): 1681-1694.
36. Raymond CR, Paul JS, Marian EQ. Handbook of Pharmaceutical Excipients 6th edition. The Pharmaceutical Press.2009:48-50, 728-731, 600-610.
37. Shejul A, Deshmane S, Biyani K. Modified Natural Carriers in Solid Dispersion for enhancement of Solubility of poorly Water Soluble Drugs. Journal of Drug Delivery and Therapeutics. 2014; 4(1): 111-116.
38. Tekade AR, Yadav JN. A Review on Solid Dispersion and Carriers Used in Therein for Solubility Enhancement of poorly Water Soluble Drugs. Advance Pharmaceutical Bulletin. 2020; 10(3): 359-369.

HOW TO CITE THIS ARTICLE

Pratibha Verma*, Seema Saini, Naresh Singh Gill. Solid Dispersion: An Update On Advanced Guide On Solubility Enhancement. International Journal of Institutional Pharmacy and Life Sciences, Vol 11[1] January-February 2021 : 01-13.